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(51) International Patent Classification ⁷ : C07D 401/12, 487/04, 455/02, A61K 31/47, 31/435	A1	(11) International Publication Number: WO 00/21952 (43) International Publication Date: 20 April 2000 (20.04.00)
(21) International Application Number: PCT/EP99/07766 (22) International Filing Date: 11 October 1999 (11.10.99) (30) Priority Data: 9822440.5 14 October 1998 (14.10.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DAVIES, David, Thomas [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). MARKWELL, Roger, Edward [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). PEARSON, Neil, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). TAKLE, Andrew, Kenneth [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).	(74) Agent: VALENTINE, Jill, Barbara; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: QUINOLINE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS (57) Abstract Piperidine derivatives and pharmaceutical derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly in man.		

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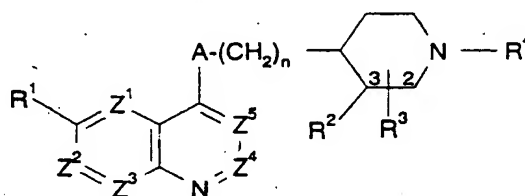
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QUINOLINE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

This invention relates to novel medicaments, being novel antibacterial compounds and compositions.

- 5 JP04095071 discloses piperidyl carbamic acid derivatives for treating dementia by ameliorating memory disturbance.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1 , Z^2 , Z^3 , Z^4 and Z^5 is N or CR^{1a} and the remainder are CH;

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R^1 is selected from hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6}) alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6}) alkyl, acyl or (C_{1-6}) alkylsulphonyl groups, NH_2CO , hydroxy, thiol, (C_{1-6}) alkylthio, heterocyclylthio, heterocyclylloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6}) alkylsulphonyloxy; (C_{1-6}) alkoxy-substituted (C_{1-6}) alkyl; halogen; (C_{1-6}) alkyl; (C_{1-6}) alkylthio; nitro; trifluoromethyl; azido; acyl; acyloxy; acylthio; (C_{1-6}) alkylsulphonyl; (C_{1-6}) alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6}) alkyl, acyl or (C_{1-6}) alkylsulphonyl groups, or when one of Z^1 , Z^2 , Z^3 , Z^4 and Z^5 is N, R^1 may instead be

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hydrogen;

R^{1a} is selected from hydrogen and the groups listed above for R^1 ;

either R^2 is hydrogen; and

- 30 R^3 is in the 2- or 3-position and is hydrogen or (C_{1-6}) alkyl or (C_{2-6}) alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C_{1-6}) alkylthio; trifluoromethyl; azido; (C_{1-6}) alkoxycarbonyl; (C_{1-6}) alkylcarbonyl; (C_{2-6}) alkenyloxycarbonyl; (C_{2-6}) alkenylcarbonyl; hydroxy

optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

or when R³ is in the 2-position it may with R⁴ form a C₃₋₅ alkylene group optionally substituted by a group R⁵ selected from:
 (C₃₋₁₂)alkyl; hydroxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkoxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkanoyloxy(C₃₋₁₂)alkyl; (C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; hydroxy-, (C₁₋₁₂)alkoxy- or (C₁₋₁₂)alkanoyloxy-(C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; cyano(C₃₋₁₂)alkyl; (C₂₋₁₂)alkenyl; (C₂₋₁₂)alkynyl; tetrahydrofuryl; mono- or di-(C₁₋₁₂)alkylamino(C₃₋₁₂)alkyl; acylamino(C₃₋₁₂)alkyl; (C₁₋₁₂)alkyl- or acyl-aminocarbonyl(C₃₋₁₂)alkyl; mono- or di-(C₁₋₁₂)alkylamino(hydroxy) (C₃₋₁₂)alkyl; optionally substituted phenyl(C₁₋₂)alkyl, phenoxy(C₁₋₂)alkyl or phenyl(hydroxy)(C₁₋₂)alkyl; optionally substituted diphenyl(C₁₋₂)alkyl; optionally substituted phenyl(C₂₋₃)alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C₁₋₂)alkyl; and optionally substituted heteroaroyl or heteroaroylmethyl;

or R³ is in the 3-position and R² and R³ together are a divalent residue =CR^{5'}R^{6'} where R^{5'} and R^{6'} are independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, aryl(C₁₋₆)alkyl and aryl(C₂₋₆)alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R³;

R⁴ forms a group with R³ as above defined or is a group -CH₂-R⁵ in which R⁵ is as defined above;

n is 0, 1 or 2; and

A is NHC(O)NH or NHC(O)O.

In one aspect the invention provides compounds of formula (I) where R¹ and R^{1a} are selected from the groups listed above other than trifluoromethyl.

The invention also provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Preferably Z¹-Z⁵ are each CH or Z¹ is N and Z²-Z⁵ are each CH.

When R¹ or R^{1a} is substituted alkoxy it is preferably (C₁₋₆)alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino, more preferably by amino or guanidino. Suitable examples of R¹ alkoxy include methoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy. Preferably R¹ is methoxy, amino(C₃₋₅)alkyloxy, guanidino(C₃₋₅)alkyloxy, nitro or fluoro, most preferably methoxy.

Preferably R^{1a} is hydrogen.

Preferably n is 0.

Preferably A is NHCONH.

R³ is preferably hydrogen, (C₁₋₆) alkyl, (C₁₋₆) alkenyl, optionally substituted 1-hydroxy-(C₁₋₆) alkyl, more preferably hydroxymethyl or 1,2-dihydroxy(C₂₋₆)alkyl wherein the 2-hydroxy group is optionally substituted. Preferred examples of R³ include hydroxymethyl, 1-hydroxyethyl or 1,2-dihydroxyethyl wherein the 2-hydroxy group is optionally substituted with alkylcarbonyl or aminocarbonyl where the amino group is optionally substituted. Other suitable examples of R³ include 2-hydroxyethyl, 2- or 3-hydroxypropyl, ethyl or vinyl.

R³ is preferably in the 3-position.

When R² and R³ together form a group, this is preferably =CHCH₃.

When R³ and R⁴ together form a group, this is preferably -(CH₂)₄- optionally substituted by R⁵. Preferably R⁵ on this cyclic group is (C₄₋₉)alkyl, unsubstituted phenyl(C₁₋₂)alkyl or unsubstituted phenyl(C₂₋₃)alkenyl, more preferably n-pentyl or n-hexyl, most preferably n-pentyl.

Suitable groups R⁴ include n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, methoxybutyl, phenylethyl, phenylpropyl or 3-phenyl-prop-2-en-yl optionally substituted on the phenyl ring, 3-benzoylpropyl, 4-benzoylbutyl, 3-pyridylmethyl, 3-(4-fluorobenzoyl)propyl, cyclohexylmethyl, cyclobutylmethyl, t-butoxycarbonylaminomethyl and phenoxyethyl.

Preferably R⁴ is (C₅₋₁₀)alkyl, unsubstituted phenyl(C₂₋₃)alkyl or unsubstituted phenyl(C₃₋₄)alkenyl, more preferably hexyl, heptyl, 5-methylhexyl, 6-methyl heptyl, 3-phenyl-prop-2-en-yl or 3-phenylpropyl, most preferably n-heptyl.

Most preferably R⁵ is unbranched at the α and, where appropriate, β positions.

Halo or halogen includes fluoro, chloro, bromo and iodo.

The term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from optionally substituted amino, halogen, (C₁₋₆)alkyl, (C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautomeric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include (C₁₋₆)alkyl optionally substituted by hydroxy, (C₁₋₆)alkoxy, thiol, (C₁₋₆)alkylthio, halo or trifluoromethyl, and amino-protecting groups such as acyl or (C₁₋₆)alkylsulphonyl groups.

The term 'heteroaryl' includes the aromatic heterocyclic groups referred to above. Examples of heteroaryl groups include pyridyl, triazolyl, tetrazolyl, indolyl, thienyl, isoimidazolyl, thiazolyl, furanyl, quinoliny, imidazolidinyl and benzothienyl.

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, (C₁₋₆)alkyl, phenyl, (C₁₋₆)alkoxy, hydroxy(C₁₋₆)alkyl, mercapto (C₁₋₆)alkyl, halo(C₁₋₆)alkyl, hydroxy, optionally substituted amino, nitro, carboxy, (C₁₋₆)alkylcarbonyloxy, (C₁₋₆)alkoxycarbonyl, formyl, or (C₁₋₆)alkylcarbonyl groups.

The term 'acyl' includes (C₁₋₆)alkoxycarbonyl, formyl or (C₁₋₆) alkylcarbonyl group.

Compounds of formula (I) wherein:

R³ is hydroxy(C₁₋₆)alkyl or 1,2-dihydroxy(C₂₋₆)alkyl optionally substituted on the hydroxy group(s) as claimed, hereinafter 'compounds of formula (IA)', are particularly preferred.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

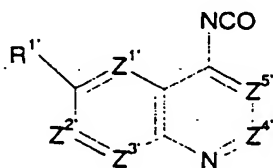
Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or salt thereof.

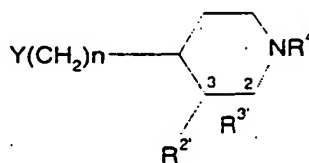
Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic or sulphuric acids, or organic acids, e.g. acetic, fumaric or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide.

Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms.

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5 , m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), and Y is OH or NH_2 in which $Z^{1'}-Z^{5'}$ are Z^1-Z^5 or groups convertible thereto, $R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ are R^1, R^2, R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $Z^{1'}-Z^{5'}$ to Z^1-Z^5 , converting $R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ to R^1, R^2, R^3 and R^4 , interconverting R^1, R^2, R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

The reaction of the compounds of formulae (IV) and (V) is a standard urea or carbamate formation reaction conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985)). The process is preferably carried out in a polar, non-nucleophilic solvent such as N,N-dimethylformamide.

$R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ are preferably R^1, R^2, R^3 and R^4 . $R^{1'}$ is preferably methoxy. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is preferably R^3 such as hydrogen, vinyl or a carboxy ester-containing group. $R^{4'}$ is preferably H or a protecting group.

Conversions of $R^{1'}, R^{2'}, R^{3'}$ and $R^{4'}$ and interconversions of R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc., 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 (C_{1-6}) alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

Examples of $Z^{1'}-Z^{5'}$ are $CR^{1a'}$ where $R^{1a'}$ is a group convertible to R^{1a} .

$R^{3'}$ alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

$R^{3'}$ carboxylate groups may be converted to R^3 hydroxymethyl by reduction with a suitable reducing agent such as lithium aluminium hydride.

R^3 1,2-dihydroxy can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see *Advanced Organic Chemistry* (Ed. March, J.) (John Wiley and Sons: 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see *Advanced Organic Chemistry* (Ed. March, J.) (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

R³ vinyl can be chain extended by standard homologation e.g by conversion to hydroxyethyl followed by oxidation to the aldehyde which is then subjected to a Wittig reaction.

Compounds of formula (I) where R² and R³ are a divalent residue =CR⁵¹R⁶¹ can be prepared by treatment of a compound of formula (I) where R³ is alken-1-yl with a strong base in an aprotic solvent. Suitable bases include Ph₂PLi/PhLi (as described in Ireland et. al., J. Amer. Chem. Soc. (1973), 7829), t-BuLi, and suitable solvents include THF and ether.

Substituents on R³ alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkylated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate.

NH is converted to NR⁴ by conventional means such as alkylation with an alkyl halide in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

It will be appreciated that under certain circumstances interconversions may interfere, for example, the piperidine NH will require protection as an acyl derivative R⁴', during coupling of the compounds of formulae (IV) and (V) and during conversion of R¹', R²' or R³'.

Compounds of formulae (IV) and (V) are known compounds) or prepared analogously.

The isocyanate of formula (IV) may be prepared conventionally. A 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) provide the isocyanate or it may be prepared more conveniently from a 4-carboxylic acid by a 'one-pot' Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori et al. *Chem. Pharm. Bull.* **35**, 2698-2704 (1987)].

The 4-carboxy derivatives are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, **6**, 324 (1957) Ed. R.C. Elderfield. Pyridazines may be prepared by routes analogous to those described in *Comprehensive Heterocyclic Chemistry*, Volume 3, Ed A.J. Boulton and A. McKillop

and naphthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942.) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride (POCl_3) or phosphorus pentachloride, PCl_5

A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride (POCl_3) or phosphorus pentachloride, PCl_5 . A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in Heterocyclic Compounds, 6, 324 (1957) Ed. R.C. Elderfield. Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and naphthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, Joe T. Adams et al., J.Amer.Chem.Soc., 1946, 68, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, J. Chem. Soc. 2100 (1955)]. For example, a 2-aminoacetophenone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

For compounds of formula (V) where Y is NH_2 suitable amines may be prepared from the corresponding acid or alcohol (Y is CO_2H or CH_2OH). In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a Curtius rearrangement and the

intermediate isocyanate can be converted to the amine by standard methods well known to those skilled in the art. For example, an acid-substituted N-protected piperidine can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, Tetrahedron Letters, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine-substituted N-protected piperidine.

In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, *Synthesis*, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (V) where $n=1$ or 2 may be prepared from the compound where $n=0$ by homologation eg starting from a compound of formula (V) where $Y=CO_2H$.

Where R_3 and R_4 form a group such as $-(CH_2)_4-$, the azabicyclic intermediate of formula (V) may be prepared from the ketone such as 1-aza-8-(equatorial)-formyloxy-bicyclo[4,4,0]decan-2-one. This ketone may be prepared by a literature procedure [H.E. Schoemaker et al. *Tetrahedron*, **34**, 163-172 (1978)] and hydrolysed to the 8-alcohol with sodium hydroxide. The alcohol may then be subjected to a Mitsunobu reaction (diethylazodicarboxylate/triphenyl phosphine) [eg. see K.Y. Ko et al. *J. Org. Chem.* **51**, 5353 (1986)] in the presence of benzoic acid to afford the 8-axial benzoate, which can be hydrolysed with sodium hydroxide in aqueous dioxan to the axial 8-hydroxy-derivative. The hydroxyl may be protected with a trimethylsilyl group and then reacted with LDA (lithium diisopropylamide) and an alkylating agent such as a haloalkane derivative e.g. 1-bromopropane, to give the 3-alkyl derivative (mixture of axial/equatorial isomers at C-3). Reduction of the lactam moiety with lithium aluminium hydride gives the required 8-(ax)-hydroxy-bicyclodecane. Homologous compounds where $n=1$ or 2 may be prepared by conventional homologation routes, for example by Wittig reaction of the above bicyclic ketone followed by reduction of the alkylene product.

Conversions of R^1 , R^2 , R^3 and R^4 may be carried out on the intermediates of formulae (IV) and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

Where a *trans*-substituted compound of formula (I) is required, a *trans*-substituted piperidine moiety of formula (V) may be prepared from the corresponding *cis* isomer of

formula (V) having an R³ vinyl group in the 3-position with a substituent that can subsequently be converted to the required group (CH₂)_nY by heating in formaldehyde.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection
5 in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral,
10 topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as
15 preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will
20 form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for
25 example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product
30 for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may
35 include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In
5 preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be
10 frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by
15 filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the
20 compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

25 No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a
30 β -lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial
35 organisms.

Example 1. 1-Aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(ax)-n-pentyl-bicyclo[4,4,0]decane

(a) 1-Aza-3-n-pentyl-8-(ax)-hydroxy-bicyclo[4,4,0]decan-2-one

5 A 1.5 M solution of lithium diisopropylamide in cyclohexane (2.25ml) was added to a solution of 1-aza-8-(ax)-(trimethylsilyloxy)-bicyclo[4,4,0]decan-2-one (0.73g) (King et al., Bioorg Med Chem Letts., vol.2, p.1147 (1992)) in dry tetrahydrofuran (10ml) at -78°C and the solution was stirred for 10 minutes. 1-Bromopropane (0.503g) was added and the solution was stirred at -78°C for 1 hour and allowed to warm up to room temperature overnight. The mixture was basified with aqueous sodium bicarbonate solution and evaporated to dryness. It was re-suspended in 1:1 tetrahydrofuran-water (100ml), acidified to pH 2 with 2 M hydrochloric acid, and stirred at room temperature for 30 minutes. The mixture was basified with 10% sodium carbonate solution, evaporated to dryness, treated with chloroform, dried over sodium sulfate and evaporated to afford an oil.

15 MS (+ve ion electrospray) m/z 240 (MH+)

(b) 1-Aza-3-n-pentyl-8-(ax)-hydroxy-bicyclo[4,4,0]decane

A solution of 1-aza-3-n-pentyl-8-(ax)-hydroxy-bicyclo[4,4,0]decan-2-one (0.3g) in dry tetrahydrofuran (5ml) was treated with lithium aluminium hydride (0.10g) and the mixture was heated under reflux for 3 hours. The cooled solution was treated dropwise with a solution of 2M sodium hydroxide until a white precipitate had formed. Dichloromethane and anhydrous sodium sulfate were added and the solution was filtered and evaporated to dryness to give an oil (0.26g).

MS (+ve ion electrospray) m/z 226 (MH+)

25

(c) Title compound

A suspension of 6-methoxyquinoline-4-carboxylic acid (0.142g) in dichloroethane (3ml) was treated with triethylamine (71mg) followed by diphenylphosphoryl azide (0.193g) and the mixture was stirred at room temperature for 1.5 hours. The resultant solution was heated (oil bath temperature 100°C) for 0.5 hours to form the isocyanate. A solution of 1-aza-3-n-pentyl-8-(ax)-hydroxy-bicyclo[4,4,0]decane (0.125g) in dichloroethane (1ml) was added and the solution was heated under reflux for 4 hours. A further batch of isocyanate [(prepared from 6-methoxyquinoline-4-carboxylic acid (47mg))] in dichloroethane was added and the solution heated under reflux for a further 1 hour, left at room temperature overnight, and evaporated to dryness. The product was dissolved in tetrahydrofuran and basified with aqueous sodium hydroxide, evaporated to dryness, and partitioned between water and

30
35

chloroform. The organic fraction was dried over sodium sulfate, evaporated and chromatographed on silica gel in ethyl acetate-hexane (1:2) to afford the title compound as a white solid (40 mg), after trituration with ether-hexane.
MS (+ve ion electrospray) m/z 426 (MH+).

5

Example 2. 1-Aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(eq)-n-pentyl-bicyclo[4,4,0]decane

Reaction of 6-methoxyquinoline-4-isocyanate prepared from 6-methoxyquinoline-4-carboxylic acid (0.142g) with 1-aza-3-n-pentyl-8-(ax)-hydroxy-bicyclo[4,4,0]decane (0.10g) (by the Method of Example 1(c)) and chromatography of the product on silica gel in ethyl acetate-hexane (1:1) gave the compound of Example 1 (30mg). Continued elution with ethyl acetate, followed by preparative TLC [methanol-ethyl acetate (1:10)] gave the title compound as a pale yellow foam (14 mg).
MS (+ve ion electrospray) m/z 426 (MH+).

15

Example 3. 1-Heptyl-4-[N-(6-methoxyquinolin-4-yl)aminocarbonyloxy]piperidine
(a) 1-Heptyl-4-hydroxypiperidine

4-Hydroxypiperidine was dissolved in N,N-dimethylformamide (20ml) and treated with potassium carbonate (1.5g, 10.8 mmol) and 1-iodoheptane (1.8 ml, 11.3 mmol).
After stirring for 2h the mixture was diluted with ethyl acetate, washed with water, brine, dried and evaporated.

(b) Title compound

6-Methoxyquinoline-4-isocyanate was prepared from the corresponding carboxylic acid (1g, 4.9 mmol) by the method of Example 1(c). 1-Heptyl-4-hydroxypiperidine (1.0g, 5.0 mmol) was added and the mixture stirred for 2.5h. After washing with sodium carbonate and brine the solution was dried and evaporated and the product purified on silica gel eluting with methanol-ethyl acetate (5:95), MH⁺ 400.

30 **Example 4. 1-Heptyl-4-(6-methoxyquinolin-4-yl)ureidopiperidine**

(a) 1-Benzyl-4-(6-methoxyquinolin-4-yl)ureidopiperidine

6-Methoxyquinoline-4-isocyanate was prepared from the corresponding carboxylic acid (1g, 4.9 mmol) by the method of Example 1(c) and 4-amino-1-benzylpiperidine (1.0 ml, 5.0 mmol) was added. After stirring for 3h the mixture was diluted with dichloromethane, washed with sodium carbonate solution, brine, dried and evaporated. Purification on silica gel eluting with methanol-ethyl acetate mixtures gave a yellow solid (0.51g, 27%) MH⁺ 391.

35

(b) Title compound

The product from Example 4(a) (0.50g, 1.28 mmol) in methanol (25 ml) was hydrogenated over 10% palladium on charcoal (0.30g) for 4 days. The mixture was filtered through celite and evaporated. The residue was dissolved in N,N-dimethylformamide (10ml) and treated with 1-iodoheptane (0.24ml, 1.5 mmol) and potassium carbonate (0.21g, 1.5 mmol). After stirring for 18h the mixture was diluted with ethyl acetate, washed with water, brine, dried and evaporated. Purification on silica gel eluting with methanol-chloroform-ammonia (5:95:0.5) gave a yellow solid (0.27g, 55%), MH⁺399.

Example 5. N-(cis-1-Heptyl-3-(R/S)-hydroxymethyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea oxalate

(a) 4-Benzylamino-1-tert-butoxycarbonyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridine
A solution of 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperidin-4-one (prepared from 3-ethoxycarbonylpiperidin-4-one and di-tert-butyl-dicarbonate in dichloromethane and triethylamine) (25g) and benzylamine (10.85g) in toluene was heated under reflux in a Dean and Stark apparatus for 18 hours and then evaporated to dryness to give an oil.

(b) cis-4-(S/R)-Benzylamino-1-tert-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine
The enamine (5a) (25g) in ethanol (300ml) was hydrogenated over platinum oxide (1.5g) for 4 days, filtered, and evaporated to dryness. It was chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound as an oil.

MS (+ve ion electrospray) m/z 363 (MH⁺).

(c) cis-4-(S/R)-Amino-1-tert-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine
The amine (5b) (4g) in ethanol (80ml) containing acetic acid (0.73g) was hydrogenated at 50psi (Parr reaction vessel) over 10% palladium-carbon (1g) for 18 hours, filtered and evaporated to dryness to afford the acetate salt of the title compound as a white solid (3g).

MS (+ve ion electrospray) m/z 273 (MH⁺).

It was converted to the oily free base by extraction using dichloromethane-sodium carbonate and drying over sodium sulfate.

(d) N-(cis-1-tert-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea

A suspension of 6-methoxyquinoline-4-carboxylic acid (0.98g) in dry toluene (50ml) was treated with triethylamine (1.95g) followed by diphenylphosphoryl azide (1.39g) and the mixture was stirred at room temperature for 8 hours. The resultant solution was treated with the amine (5c) and then heated under reflux for 4 hours and

evaporated to dryness. The product was chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound (1.98g) as a foam.

MS (+ve ion electrospray) m/z 473 (MH+).

(e) N-(cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea

- 5 The urea (5d) (1.0g) was treated with dichloromethane (30ml) and trifluoroacetic acid (20ml) at room temperature for 3 hours and evaporated to dryness. It was basified with sodium carbonate solution and evaporated to dryness. The solid was extracted three times with ethanol-chloroform (1:9) and evaporated to dryness to afford a foam (0.75g). MS (+ve ion electrospray) m/z 373 (MH+).

- 10 (f) N-(cis-3-(R/S)-Ethoxycarbonyl-1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea oxalate

- The amine (5e) (0.75g) in dry ethanol (15ml) was treated with heptaldehyde (0.636g) and sodium triacetoxyborohydride (0.459g) for 1 hour at room temperature. Sodium bicarbonate solution was added and the mixture was extracted with
15 dichloromethane, dried over sodium sulfate, and evaporated to afford an oil. Chromatography on silica gel (ethyl acetate-hexane) gave the title compound (0.68g) as an oil.

MS (+ve ion electrospray) m/z 471 (MH+).

- The free base in dichloromethane was treated with 1 molar equivalent of oxalic acid in
20 ether and the resulting solid was collected, triturated with ether, to afford the oxalate salt as a white solid.

(g) Title compound

- The ester (5f) (0.12g) in dry tetrahydrofuran (4ml) at 0°C was treated with lithium aluminium hydride (0.655ml of a 1M solution in ether) for 5 hours, and at room
25 temperature for 1 hour, then it was quenched by the addition of 2M sodium hydroxide. Dichloromethane and sodium sulfate were added and the solution was filtered and evaporated to dryness. The product was chromatographed on silica gel (methanol-dichloromethane) to afford the title compound (0.055g), as the oily free base. MS (+ve ion electrospray) m/z 429 (MH+).

- 30 The free base in dichloromethane was converted to the oxalate salt in the normal manner, affording a white solid.

Example 6. N-(cis-1-Heptyl-3-(R/S)-hydroxymethyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]naphthyridin-4-yl)urea oxalate

- 35 (a) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester

 3-Amino-6-methoxypyridine (12.41 g) and diethyl ethoxymethylene malonate (20.2 ml) in Dowtherm A (400 ml) were heated at reflux, under argon for 1 hour. The

cooled reaction mixture was poured into pentane (1 litre). The precipitated solid was collected by filtration, washed with pentane and dried to afford a solid (24.78 g, crude).

(b) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid

5 The ester (6a) (0.642g) in 10% aqueous sodium hydroxide (115 ml) was heated at reflux for 1.5 hours. The reaction mixture was cooled then acidified with glacial acetic acid. The precipitated solid was collected by filtration, washed with water and dried *in vacuo* to afford a beige solid (0.542g).

MS (+ve ion electrospray) m/z 221 (MH^+).

(c) 4-Chloro-6-methoxy-[1,5]naphthyridine

10 The acid (6b) (6.82 g) was heated in quinoline (20ml) at reflux for 2 hours, the mixture was cooled and poured into ether (200ml) and the orange solid was filtered and washed with ether (5 x 200ml). A sample (3.87g) of the dried solid was treated with phosphorus oxychloride (30ml) at room temp for 3 hours, the solvent was removed *in vacuo* and the residue quenched with crushed ice (200g). The mixture was basified with ammonia solution and filtered. The solid was washed with dichloromethane (10 x 100ml), which was evaporated and chromatographed on silica gel (dichloromethane as eluent) to give a yellow solid (3.0g).

MS (+ve ion electrospray) m/z 195, 197 (MH^+).

(d) 4-Amino-6-methoxy-[1,5]naphthyridine

20 A solution of the chloro compound (6c) (2.0g) in pyridine (30ml) was treated with *n*-propylamine hydrochloride (6.0g) and the mixture heated at reflux for 16 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The aqueous phase was washed with ethyl acetate, the combined organics dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by chromatography on silica gel (5-10% methanol in dichloromethane) afforded a yellow solid (1.0g).

1H NMR ($CDCl_3$) δ : 4.05 (3H, s), 5.36 (2H, bs), 6.71 (1H, d, $J=5$ Hz), 7.08 (1H, d, $J=9$ Hz), 8.10 (1H, d, $J=9$ Hz), 8.40 (1H, d, $J=5$ Hz).

MS (+ve ion electrospray) m/z : 176 (MH^+).

30 (e) N-(cis-1-tert-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea

To a solution of amine (6d) (0.5g) in chloroform (4ml) was added 1,1'-carbonyldiimidazole (0.76g) and dimethylaminopyridine (0.38g) and the solution was stirred at room temperature for 3.5 hours and evaporated to dryness. The product was heated at 100°C in dry DMF (7ml) containing the amine (5c) (0.85g), for 3 hours.

35 Aqueous sodium carbonate was added and the mixture was extracted with dichloromethane, dried over sodium sulfate, and evaporated to afford a foam. Chromatography on silica gel (ethyl acetate-hexane) gave an oil (0.928g).

MS (+ve ion electrospray) m/z 474 (MH+).

(f) N-(cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridine-4-yl)urea

5 The urea (6e) (0.92g) was treated with dichloromethane (20ml) and trifluoroacetic acid (30ml) at room temperature for 3 hours and evaporated to dryness. It was basified with sodium carbonate solution and evaporated to dryness. The solid was extracted three times with warm ethanol-chloroform (1:9) and evaporated to dryness to afford a foam (0.80g).

MS (+ve ion electrospray) m/z 374 (MH+).

10 (g) N-(cis-3-(R/S)-Ethoxycarbonyl-1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea oxalate

The amine (6f) (0.80g) in dry ethanol (20ml) was treated with heptaldehyde (0.26g) and sodium triacetoxymethylborohydride (0.82g) for 1 hour at room temperature. Sodium bicarbonate solution was added and the mixture was extracted with
15 dichloromethane, dried over sodium sulfate, and evaporated to afford an oil. Chromatography on silica gel (ethyl acetate-hexane) gave the title compound (0.72g) as an oil.

MS (+ve ion electrospray) m/z 472 (MH+).

20 The free base in dichloromethane was treated with 1 molar equivalent of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the oxalate salt as a white solid.

(h) Title compound

25 The ester (6g) (0.10g) in dry tetrahydrofuran (7ml) was treated with lithium aluminium hydride (0.42ml of a 1M solution in ether) at 0°C for 1.5 hours and at room temperature for 2 hours, then it was quenched by the addition of 2M sodium hydroxide. Dichloromethane and sodium sulfate were added and the solution was filtered and evaporated to dryness. The product was chromatographed on silica gel (methanol-dichloromethane) to afford the title compound (0.074g), as the oily free base.

MS (+ve ion electrospray) m/z 430 (MH+).

30 ¹H NMR (CDCl₃) δ: 0.88 (3H, t), 1.20 (9H, bs), 1.40 (2H, bs), 1.9 – 2.4 (6H, m), 2.50 (1H, bd), 2.90 (2H, m), 3.90 (2H, m), 4.10 (3H, s), 4.17 (1H, m), 6.60 (1H, bd), 7.10 (1H, d), 8.20 (1H, d), 8.38 (1H, d), 8.61 (1H, d), 8.78 (1H, s).

35 The free base in dichloromethane was converted to the oxalate salt in the normal manner, affording a white solid.

Example 7. N-(1-Heptyl-4-piperidyl-N'-(6-methoxy-1,5-naphthyridin-4-yl)urea oxalate

A solution of the amine (6d) (0.08, 0.5 mmol) in chloroform (2ml) was treated with N,N-dimethylaminopyridine (0.06g, 0.5 mmol) then 1,1'-carbonyldiimidazole (0.11g, 0.7 mmol). After 2 hours the chloroform was removed by evaporation and the residue treated with a solution of 4-amino-1-heptylpiperidine (0.1g, 0.5 mmol) in N,N-dimethylformamide (1 ml) and the mixture heated to 100 °C for 1 hour. Water (2ml) was added dropwise and filtration gave a white solid. Chromatography on silica eluting with a methanol in ethyl acetate gradient afforded the title compound as a white solid, (0.1g, 50%).
¹H NMR (CD₃OD) 0.80 (3H, t), 1.20 (8H, m), 1.50 (4H, m), 1.90 (2H, m), 2.10 (2H, m), 2.25 (2H, m), 2.85 (2H, m), 3.55 (1H, m), 4.00 (3H, s), 7.10 (1H, d), 8.00 (1H, d), 8.20 (1H, d), 8.35 (1H, d).

The following example was prepared by procedures analogous to those described herein:

Example 8. 1-Aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(ex)-n-hexyl-bicyclo[4,4,0]decane**Biological Activity**

The MIC (µg/ml) of compounds 1, 3 and 4 against various organisms was determined.

Examples 1, 5, 6 and 7 have an MIC of less than or equal to 1µg/ml against one or more of a range of gram positive and gram negative bacteria.

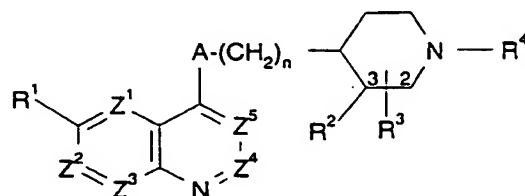
The remaining compounds 2, 3, 4 and 8 showed an MIC of less than or equal to 16µg/ml against one or more of a range of gram positive and gram negative bacteria. (See table 1).

TABLE 1

Organism	Example 1	Example 3	Example 4	Example 5	Example 6	Example 7
<i>S. aureus</i> Oxford	2	8	16	1	0.5	1
<i>S. aureus</i> WCUH29	4	4	8	1	1	1
<i>S. aureus</i> Carter 37	8	8	16	ND	ND	ND
<i>E. faecalis</i> I	8	8	8	4	8	8
<i>M. catarrhalis</i> Ravasio	32	16	ND	ND	ND	ND
<i>S. pneumoniae</i> R6	1	4	2	ND	ND	ND

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1 , Z^2 , Z^3 , Z^4 and Z^5 is N or CR^{1a} and the remainder are CH;

- 10 R^1 is selected from hydroxy; (C₁₋₆) alkoxy optionally substituted by (C₁₋₆)alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, NH₂CO, hydroxy, thiol, (C₁₋₆)alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C₁₋₆)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted (C₁₋₆)alkyl; halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; nitro; trifluoromethyl; azido; acyl; acyloxy; acylthio; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, or when one of Z^1 , Z^2 , Z^3 , Z^4 and Z^5 is N, R^1 may instead be hydrogen;

20

R^{1a} is selected from hydrogen and the groups listed above for R^1 ;

either R^2 is hydrogen; and

- 25 R^3 is in the 2- or 3-position and is hydrogen or (C₁₋₆)alkyl or (C₂₋₆)alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C₁₋₆)alkylthio; trifluoromethyl; azido; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl

- 30 wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl.

(C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenylloxycarbonyl or (C₂₋₆)alkenylcarbonyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

or when R³ is in the 2-position it may with R⁴ form a C₃₋₅ alkylene group optionally substituted by a group R⁵ selected from:

(C₃₋₁₂)alkyl; hydroxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkoxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkanoyloxy(C₃₋₁₂)alkyl; (C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; hydroxy-, (C₁₋₁₂)alkoxy- or (C₁₋₁₂)alkanoyloxy-(C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; cyano(C₃₋₁₂)alkyl; (C₂₋₁₂)alkenyl; (C₂₋₁₂)alkynyl; tetrahydrofuryl; mono- or di-(C₁₋₁₂)alkylamino(C₃₋₁₂)alkyl; acylamino(C₃₋₁₂)alkyl; (C₁₋₁₂)alkyl- or acyl-aminocarbonyl(C₃₋₁₂)alkyl; mono- or di-(C₁₋₁₂)alkylamino(hydroxy) (C₃₋₁₂)alkyl; optionally substituted phenyl(C₁₋₂)alkyl, phenoxy(C₁₋₂)alkyl or phenyl(hydroxy)(C₁₋₂)alkyl; optionally substituted diphenyl(C₁₋₂)alkyl; optionally substituted phenyl(C₂₋₃)alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C₁₋₂)alkyl; and optionally substituted heteroaryl or heteroarylmethyl;

or R³ is in the 3-position and R² and R³ together are a divalent residue =CR^{5¹}R^{6¹} where R^{5¹} and R^{6¹} are independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, aryl(C₁₋₆)alkyl and aryl(C₂₋₆)alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R³;

R⁴ forms a group with R³ as above defined or is a group -CH₂-R⁵ in which R⁵ is as defined above;

n is 0, 1 or 2; and

A is NHC(O)NH or NHC(O)O.

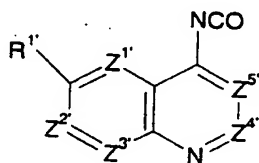
2. A compound according to claim 1 wherein Z¹-Z⁵ are each CH or Z¹ is N and Z²-Z⁵ are each CH.

3. A compound according to claim 1 or 2 wherein R¹ is methoxy, amino(C₃₋₅)alkyloxy, guanidino(C₃₋₅)alkyloxy, nitro or fluoro.

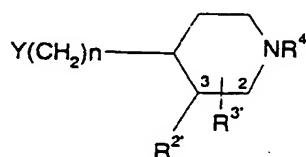
4. A compound according to any preceding claim wherein A is NHCONH and n is 0.

5. A compound according to any preceding claim wherein R^3 is in the 3-position and is hydroxy(C_{1-6})alkyl or 1,2-dihydroxy(C_{2-6})alkyl optionally substituted on the hydroxy group(s).
6. A compound according to any preceding claim wherein R^4 is (C_{5-10})alkyl, unsubstituted phenyl(C_{2-3})alkyl or unsubstituted phenyl(C_{3-4})alkenyl.
7. A compound according to claim 1 selected from:
- 1-aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(ax)-n-pentyl-bicyclo[4,4,0]decane;
- 1-aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(eq)-n-pentyl-bicyclo[4,4,0]decane;
- 1-heptyl-4-[N-(6-methoxyquinolin-4-yl)aminocarbonyloxy]piperidine
- 1-heptyl-4-(6-methoxyquinolin-4-yl)ureidopiperidine;
- N-(cis-1-heptyl-3-(R/S)-hydroxymethyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea;
- N-(cis-1-heptyl-3-(R/S)-hydroxymethyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea;
- N-(1-heptyl-4-piperidyl)-N'-(6-methoxy-1,5-naphthyridin-4-yl)urea;
- 1-aza-8-(ax)-[(6-methoxyquinolin-4-yl)-aminocarbonyloxy]-3-(ex)-n-hexyl-bicyclo[4,4,0]decane;
- or a pharmaceutically acceptable derivative of any of the foregoing compounds.

8. A process for preparing a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

- wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 , m , n , R^1 , R^2 , R^3 and R^4 are as defined in formula (I), and Y is OH or NH_2 in which $Z^{1'}-Z^{5'}$ are Z^1-Z^5 or groups convertible thereto, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^1 , R^2 , R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $Z^{1'}-Z^{5'}$ to Z^1-Z^5 , converting $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

9. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1, and a pharmaceutically acceptable carrier.
10. A method of treatment of bacterial infections in mammals, particularly in man,
5 which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1.
11. The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1 in the manufacture of a medicament for use in the
10 treatment of bacterial infections in mammals.
12. A pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D487/04 C07D455/02 A61K31/47 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 387 510 A (BAYER) 19 September 1990 (1990-09-19) page 9, line 33 - line 39; claims; examples	1-12
A	US 4 472 404 A (PAXTON ET. AL.) 18 September 1984 (1984-09-18) claims; examples	1-12
A	EP 0 497 303 A (KYORIN PHARMACEUTICAL CO. LTD.) 5 August 1992 (1992-08-05) claims; examples	1-12
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

03.03.00

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/EP 99/07766

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Week 9219 Derwent Publications Ltd., London, GB; AN 1992-156268 XP002130005 & JP 04 095071 A (KYORIN PHARMACEUTICAL CO. LTD.), 27 March 1992 (1992-03-27) abstract</p>	1-12
A	<p>CHEMICAL ABSTRACTS, vol. 71, no. 21, 24 November 1969 (1969-11-24) Columbus, Ohio, US; abstract no. 101730j, HAMANA, M. ET. AL.: "Quinolinecarbamates, bactericides and fungicides." page 337; column 1; XP002130004 abstract & JP 69 018299 A (KOWA CO. LTD.)</p>	1-12
P, X	<p>WO 99 37635 A (SMITHKLINE BEECHAM) 29 July 1999 (1999-07-29) claims; examples</p>	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/07766

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 387510 A	19-09-1990	JP 2235869 A	18-09-1990
US 4472404 A	18-09-1984	NONE	
EP 497303 A	05-08-1992	JP 5058999 A	09-03-1993
		AU 643590 B	18-11-1993
		AU 1064992 A	06-08-1992
		CN 1064075 A	02-09-1992
		DE 69225625 D	02-07-1998
		DE 69225625 T	28-01-1999
		ES 2118094 T	16-09-1998
		KR 9609429 B	19-07-1996
		CA 2060393 A	01-08-1993
		US 5300515 A	05-04-1994
JP 04095071 A	27-03-1992	NONE	
JP 69018299 A		NONE	
WO 9937635 A	29-07-1999	AU 2717899 A	09-08-1999

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